INTERIM UPDATE

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INTERIM UPDATE: This Practice Bulletin is updated to reflect limited, focused changes in the recommendations for cervical cancer screening in adolescents and young women who are infected with human immunodeficiency virus or who are otherwise immunocompromised.

Cervical Cancer Screening and Prevention

The incidence of cervical cancer in the United States has decreased more than 50% in the past 30 years because of widespread screening. In 1975, the rate was 14.8 per 100,000 women. By 2011, it decreased to 6.7 per 100,000 women. Mortality from the disease has undergone a similar decrease from 5.55 per 100,000 women in 1975 to 2.3 per 100,000 women in 2011 (1). The American Cancer Society (ACS) estimated that there would be 12,900 new cases of cervical cancer in the United States in 2015, with 4,100 deaths from the disease (2). Cervical cancer is much more common worldwide, particularly in countries without screening programs, with an estimated 527,624 new cases of the disease and 265,672 resultant deaths each year (3). When cervical cancer screening programs have been introduced into communities, marked reductions in cervical cancer incidence have followed (4, 5).

New technologies for cervical cancer screening continue to evolve, as do recommendations for managing the results. In addition, there are different risk–benefit considerations for women at different ages, as reflected in age-specific screening recommendations. In 2011, the ACS, the American Society for Colposcopy and Cervical Pathology (ASCCP), and the American Society for Clinical Pathology (ASCP) updated their joint guidelines for cervical cancer screening (6), as did the U.S. Preventive Services Task Force (USPSTF) (7). Subsequently, in 2015, ASCCP and the Society of Gynecologic Oncology (SGO) issued interim guidance for the use of a human papillomavirus (HPV) test for primary screening for cervical cancer that was approved in 2014 by the U.S. Food and Drug Administration (FDA) (8). The purpose of this document is to provide a review of the best available evidence regarding the prevention and early detection of cervical cancer.

Background

Most cases of cervical cancer occur in women who were either never screened or were screened inadequately (9, 10). Estimates suggest that 50% of the women in whom cervical cancer is diagnosed never had cervical cytology testing, and another 10% had not been screened within the 5 years before diagnosis (11–13). Additional public health measures remain critical to improving access to screening for this group of women, who often are uninsured or underinsured. Although rates of cervical cancer are decreasing in women born in the United States who have access to screening, women who are immigrants to the United States, those lacking a regular source of health care, and the uninsured are at especially high risk (14).

Natural History of Cervical Neoplasia

Human papillomavirus is divided into two classes: 1) oncogenic and 2) nononcogenic. Infection with oncogenic (or high-risk) HPV usually is a necessary but not sufficient factor for the development of squamous cervical neoplasia. Therefore, only a small fraction of women infected with high-risk HPV will develop significant cervical abnormalities and cancer. The current model of cervical carcinogenesis posits that HPV infection results in either transient or persistent infection (15, 16).

Most HPV infection is transient and poses little risk of progression. Only a small fraction of infections are persistent, but persistent infection at 1 year and 2 years after initial infection strongly predicts subsequent risk of cervical intraepithelial neoplasia (CIN) 3 or cancer regardless of age (6, 17, 18).

Factors that determine which HPV infections will persist are incompletely understood. The HPV genotype appears to be the most important determinant of persistence and progression. Human papillomavirus-16 has the highest carcinogenic potential and accounts for approximately 55–60% of all cases of cervical cancer worldwide. Human papillomavirus-18 is the next most carcinogenic genotype and is responsible for 10–15% of cases of cervical cancer. Approximately 12 other genotypes are associated with the remainder of cases of cervical cancer (19–21). Known cofactors that increase the likelihood of persistent HPV infection include cigarette smoking, a compromised immune system, and human immunodeficiency virus (HIV) infection (22, 23). Human papillomavirus infection is most common in teenagers and women in their early 20s, with a decrease in prevalence as women age (24–27). Most young women, especially those younger than 21 years, have an effective immune response that clears the infection in an average of 8 months or decreases the viral load to undetectable levels (in 85–90% of women) in an average of 8–24 months (28–34). Concomitant with infection resolution, most cervical neoplasia also will resolve spontaneously in this population (33–38).

The natural course of an HPV infection does not appear to vary with age in women aged 30–65 years (39). Newly acquired HPV infection appears to have the same low chance of persistence regardless of age in women 30 years and older (39). However, HPV infection detected in women older than 30 years is more likely to reflect persistent infection. This correlates with increasing rates of occurrence of high-grade squamous intraepithelial lesions (HSILs) with increasing age (39).

Given that low-grade neoplasia (or CIN 1) is a manifestation of acute HPV infection, there is a high rate of regression to normal histology results, leading to current recommendations for observation rather than treatment of these cases (40). The clinical approach to CIN 2 is currently controversial because of the challenge in accurate diagnosis as well as the uncertainty about ideal management. The diagnosis of CIN 2 has a high degree of interobserver variability. Furthermore, the prognosis of CIN 2 lesions seems to represent a mix of low-grade and high-grade lesions that cannot be differentiated easily by histology, rather than representing a specific intermediate lesion (41, 42). Concerns about the limitations of the CIN 2 categorization led the ASCCP and the College of American Pathologists to adopt a revised two-tiered histologic classification (low-grade squamous intraepithelial lesions [LSILs] and HSILs), which eliminated CIN 2 as a separate category (43). In a cohort of untreated patients with CIN 3, the cumulative incidence of invasive cancer was reported to be 30.1% at 30 years, which is evidence that CIN 3 poses a significant risk of progression to cancer (44).

In evaluating appropriate screening intervals, it is important to consider the time required for disease progression. Most HPV-related types of cervical neoplasia progress very slowly. Time from development of CIN 3 to cancer is not precisely known, but the 10-year difference in age of diagnosis between screen-detected CIN 3 and cancer suggests long average sojourn time in the precancerous state (23). This rather indolent disease course is well suited to less frequent testing (ie, at intervals longer than 1 year).

Cervical Cytology Screening Techniques

Liquid-based and conventional methods of cervical cytology specimen collection are acceptable for screening. Exfoliated cells are collected from the transformation zone of the cervix and transferred to a vial of liquid preservative that is processed in the laboratory (liquid-based technique) or transferred directly to a slide and fixed (conventional technique). Blood, discharge, and some lubricants (including personal lubricants used by patients) may interfere with specimen interpretation. Use of a small amount of water-based lubricant with speculum examination has been shown to decrease examination discomfort compared with use of water alone (45–47). At least one manufacturer has a list of lubricants that have been confirmed not to contain interfering substances (48–50). If a water-based lubricant is used, it is important to minimize the amount that comes into contact with the cervix and to choose one that is consistent with the recommendations of the manufacturer of the liquid-based collection kit. A small amount of water-soluble lubricant on the speculum does not decrease the quality of cervical cytology test results. Four published randomized controlled trials that assessed the effect of lubrication on conventional cytology demonstrated no effect on the quality of cervical cytology test results (51–55). Use of a large amount of lubricant applied directly to the cervix (ie, a 1–1.5-cm ribbon of lubricant directly applied to the cervical os) can affect specimen adequacy (50), but this is not standard clinical practice. In a retrospective review of 4,068 liquid-based Pap test specimens, 0.4% had obscuring material that caused misinterpretation of results, with roughly one half of these cases possibly related to lubricant use (49).

The liquid-based method of cervical cytology specimen collection has the advantage of allowing a single specimen to be used to perform cytology, HPV testing, and testing for gonorrhea and chlamydial infection. Despite several theoretic advantages of the liquid-based technique, including easier interpretation, filtering of blood and debris, and fewer unsatisfactory results, a meta-analysis of eight studies and a randomized trial did not show an appreciable difference in sensitivity or specificity for the detection of CIN compared with the conventional cervical cytology screening technique (56, 57).

Cytologic Test Result Reporting

The Bethesda System of cervical cytologic test result reporting generally is accepted in the United States (see Box 1). It has undergone three revisions since 1988 (58).

Box 1. The 2014 Bethesda System for Reporting Cervical Cytology ⇐

Specimen Type
Indicate: conventional test (Pap test), liquid-based preparation, or other.

Specimen Adequacy
- Satisfactory for evaluation (describe presence or absence of endocervical/transformation zone component and any other quality indicators, eg, partially obscuring blood, inflammation)
- Unsatisfactory for evaluation (specify reason)
  – Specimen rejected or not processed (specify reason)
  – Specimen processed and examined, but unsatisfactory for evaluation of epithelial abnormality because of (specify reason)

General Categorization (Optional)
- Negative for intraepithelial lesion or malignancy
- Other: see *Interpretation/Result* (eg, endometrial cells in a woman 45 years of age or older)
- Epithelial cell abnormality: see *Interpretation/Result* (specify "squamous" or "glandular" as appropriate)

Interpretation/Result
- Negative for intraepithelial lesion or malignancy (when there is no cellular evidence of neoplasia, state this in the *General Categorization* section, in the *Interpretation/Result* section, or both—whether or not there are organisms or other non-neoplastic findings)
  – Nonneoplastic findings (optional to report; list not inclusive)
    ▪ Nonneoplastic cellular variations
      ▸ Squamous metaplasia
      ▸ Keratotic changes
      ▸ Tubal metaplasia
      ▸ Atrophy
      ▸ Pregnancy-associated changes
    ▪ Reactive cellular changes associated with
      ▸ Inflammation (includes typical repair)
        ○ Lymphocytic (follicular) cervicitis
      ▸ Radiation
      ▸ Intrauterine device
    ▪ Glandular cells status posthysterectomy
  – Organisms
    ▪ *Trichomonas vaginalis*
    ▪ Fungal organisms morphologically consistent with *Candida* species
    ▪ Shift in flora suggestive of bacterial vaginosis
    ▪ Bacteria morphologically consistent with *Actinomyces* species

(continued)

Box 1. The 2014 Bethesda System for Reporting Cervical Cytology *(continued)*

Interpretation/Result (continued)

• Negative for intraepithelial lesion or malignancy *(continued)*
    – Organisms *(continued)*
        ■ Cellular changes consistent with herpes simplex virus
        ■ Cellular changes consistent with cytomegalovirus
• Other
    – Endometrial cells (in a woman 45 years of age or older) (specify if "negative for squamous intraepithelial lesion")
• Epithelial cell abnormalities
    – Squamous cell
        ■ Atypical squamous cells (ACS)
            ◗ Of undetermined significance (ASC-US)
            ◗ Cannot exclude high-grade squamous intraepithelial lesion (HSIL) (ASC-H)
        ■ Low-grade squamous intraepithelial lesion (LSIL) (encompassing: human papillomavirus/mild dysplasia/cervical intraepithelial neoplasia (CIN) 1
        ■ High-grade squamous intraepithelial lesion (encompassing: moderate and severe dysplasia, carcinoma in situ; CIN 2, and CIN 3)
            ◗ With features suspicious for invasion (if invasion is suspected)
        ■ Squamous cell carcinoma
    – Glandular cell
        ■ Atypical
            ◗ Endocervical cells (not otherwise specified or specify in comments)
            ◗ Endometrial cells (not otherwise specified or specify in comments)
            ◗ Glandular cells (not otherwise specified or specify in comments)
        ■ Atypical
            ◗ Endocervical cells, favor neoplastic
            ◗ Glandular cells, favor neoplastic
        ■ Endocervical adenocarcinoma in situ
        ■ Adenocarcinoma
            ◗ Endocervical
            ◗ Endometrial
            ◗ Extrauterine
            ◗ Not otherwise specified
• Other malignant neoplasms (specify)

Adjunctive Testing

Provide a brief description of the test method(s) and report the result so that it is easily understood by the clinician.

Computer-Assisted Interpretation of Cervical Cytology

If case examined by an automated device, specify device and result.

Educational Notes and Comments Appended to Cytology Reports (Optional)

Suggestions should be concise and consistent with clinical follow-up guidelines published by professional organizations (references to relevant publications may be included).

Reprinted from Nayar R, Wilbur DC, editors. The Bethesda system for reporting cervical cytology: definitions, criteria, and explanatory notes. 3rd ed. New York (NY): Springer; 2015. With permission of Springer.

Human Papillomavirus Testing

Several tests have been approved by the FDA for the detection of cervical HPV. They assess exfoliated cervical cells for the presence of subsets of the 15–18 potentially cancer-causing (high-risk) HPV genotypes (59). Most test for 13–14 of the most common high-risk genotypes. These test kits should be used according to their FDA-approved labeling, be validated, and meet specific criteria for clinical performance (60–62). Liquid-based cytology and HPV tests are FDA approved for use with specific sample collection media. Only FDA-approved media should be used for HPV tests because unapproved media may provide false results under certain conditions. The indications for HPV testing include the following:

- Determination of the need for colposcopy in women with an ASC-US cytology result ("reflex testing")

- Use as an adjunct to cytology for cervical cancer screening in women aged 30–65 years and older ("cotesting")

- One HPV test was FDA approved in 2014 for primary cervical cancer screening in women 25 years and older

Testing should be performed only to detect the presence of high-risk HPV. There is no role for testing for low-risk genotypes, and tests for low-risk HPV should not be performed (40). All references to HPV testing in this document are to testing for high-risk HPV. Major society guidelines include some off-label uses, such as follow-up after treatment. Off-label use should be restricted to those indications described in major society, peer-reviewed guidelines (6, 40).

Human Papillomavirus Genotyping

There are commercially available, FDA-approved HPV genotyping tests for HPV-16, HPV-18, or the two in combination. Guidelines support the use of HPV genotyping for women aged 30–65 years who are undergoing cotesting and have negative Pap test results but positive high-risk HPV test results (40).

Human Papillomavirus Vaccination

The introduction of vaccines targeting the most common cancer-causing HPV genotypes has advanced the primary prevention of cervical cancer. In Australia, which has a population-based vaccination program with high adherence, a decrease in high-grade cervical abnormalities was noted within 3 years after program implementation (63). The FDA has approved three vaccines shown to be effective at preventing HPV infection: 1) a bivalent vaccine, which covers HPV-16 and HPV-18; 2) a quadrivalent vaccine, which in addition to HPV-16 and HPV-18 also covers HPV-6 and HPV-11; and 3) a 9-valent vaccine approved in 2014, which covers an additional five high-risk HPV genotypes. The bivalent and quadrivalent vaccines offer limited cross-protection against approximately 30% of cases of cervical cancer caused by HPV genotypes other than HPV-16 and HPV-18 (20, 64). The 9-valent vaccine covers approximately 20% more high-risk HPV infections caused by the five additional HPV genotypes (65). The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention and the American College of Obstetricians and Gynecologists recommend administration of the vaccine to females aged 9–26 years (66, 67). The Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents recommends vaccinating HIV-infected females aged 9–26 years (68). The Panel and ACIP advocate vaccinating girls before they reach an age at which they may be exposed to HPV. However, many women will receive the vaccine when they are older and after viral exposure. It is predicted that significant reduction in the number of cases of cervical cancer likely will not begin until approximately 20 years after widespread vaccination (69). At this time, cervical cancer screening remains the best approach to protect women from cervical cancer, and screening recommendations apply regardless of HPV vaccination status (6).

Revaccination with the 9-valent HPV vaccine in individuals who previously completed the three-dose series with the bivalent HPV vaccine or the quadrivalent HPV vaccine currently is not a routine recommendation (67). If the HPV vaccination series already has been initiated in a female patient, the series may be completed with any HPV vaccine product (66). Thus, given the high degree of protection with any HPV vaccine and the risk of viral infection in unvaccinated women, eligible patients should be vaccinated with whichever vaccine is readily available to them, and vaccination should not be delayed to obtain a specific vaccine type.

Balancing Benefits and Risks in Cervical Cancer Prevention

Protection from cervical cancer is the primary goal of screening, but as the prevalence of the disease decreases, other considerations may become equally important in the decision-making process. For example, the effects of invasive diagnostic workups (eg, colposcopy and biopsy) and overtreatment of lesions likely to regress have adverse consequences related to costs and potentially to reproductive outcomes. In addition, the anxiety

and stigma associated with HPV infection are significant concerns for women who participate in cervical cancer screening programs (70–72).

Cervical cancer screening guidelines have been revised several times in the past decade, and the differences in the lifetime risk of cervical cancer are small across these screening strategies. Because most cervical cancer detected through screening is found in the early stages, life expectancy differences are even smaller because survival is high (1). The recent revisions have balanced cancer detection with harms of screening by incorporating the powerful negative predictive value of HPV testing and lengthening screening intervals. Current guidelines are based on achieving the benchmark cancer risk that would be achieved by performing cervical cytology every 3 years. Lower risks of cancer are achievable with more frequent screening but would require more diagnostic evaluations, patient inconvenience, cost, and other harms of screening. The screening interval with the appropriate balance between benefits and harms is currently a matter of active discussion (73). Incorporating a discussion of the benefits as well as the potential harms of screening into patient conversations will help to inform clinical decision making and allow for inclusion of the patient's preferences in the process.

Clinical Considerations and Recommendations

▶ *When should screening begin?*

Cervical cancer screening should begin at age 21 years. With the exception of women who are infected with HIV or who are otherwise immunocompromised, women younger than 21 years should not be screened regardless of the age of sexual initiation or the presence of other behavior-related risk factors (Table 1) (6). The recommendation to start screening at age 21 years regardless of the age of onset of sexual intercourse is based on the very low incidence of cancer and the lack of data that screening is effective in this age group (74, 75). Only 0.1% of cases of cervical cancer occur before age 20 years (1), which translates to approximately 1–2 cases per year per 1,000,000 females aged 15–19 years (1, 76). Further, studies from the United States and the United Kingdom have demonstrated that screening younger women has not decreased their rate of cervical cancer (74, 77).

Human papillomavirus infection is commonly acquired by young women shortly after the initiation of vaginal intercourse (30, 31, 33, 34, 77, 78) and other sexual activity (79). Nearly all cases are cleared by the immune system within 1–2 years without producing neoplastic changes (23, 32, 33, 35–38). Although cancer is rare in adolescents, neoplasia is not. In a report of 10,090 Pap test results in females aged 12–18 years, 422 specimens (5.7%) were reported as LSIL and only 55 specimens (0.7%) were HSIL (80).

Earlier onset of screening than recommended may increase anxiety, morbidity, and expense and lead to overuse of follow-up procedures. The emotional effect of labeling an adolescent with a sexually transmitted infection and potential precancer must be considered because adolescence is a time of heightened concern for self-image and emerging sexuality. Studies have documented a significant increase in rates of preterm birth among women previously treated with excisional procedures for neoplasia (81). However, in one systematic review and meta-analysis, this increased risk was observed only when women who underwent such procedures were compared with women with no history of abnormal cervical cytology or colposcopy results (82). Avoiding unnecessary excision or ablation of the cervix in young women clearly is advisable, even though the association between loop electrosurgical excision procedure and preterm birth has been challenged (83).

Initiation of reproductive health care should not be predicated on cervical cancer screening (84). Important strategies for preventing cervical cancer in women younger than 21 years include HPV vaccination and counseling about safe-sex practices to limit exposure to sexually transmitted infections.

▶ *What tests should be performed for screening?*

Women aged 21–29 years should be tested with cervical cytology alone, and screening should be performed every 3 years. Cotesting should not be performed in women younger than 30 years. For women aged 30–65 years, cotesting with cytology and HPV testing every 5 years is preferred; screening with cytology alone every 3 years is acceptable. Liquid-based and conventional methods of cervical cytology collection are acceptable for screening (6). These screening recommendations are not meant for women with cervical cancer or those who have HIV infection, are immunocompromised, or were exposed to diethylstilbestrol in utero. Since the publication of the 2011 joint ACS, ASCCP, and ASCP guidelines and the USPSTF guidelines, a test for primary HPV testing has been approved by the FDA and is discussed separately (see "*What is the role for cervical cancer screening with HPV testing alone?*").

Human papillomavirus testing is more sensitive but less specific than cervical cytology (85). In the 2011 joint ACS, ASCCP, and ASCP guidelines and the USPSTF guidelines, cotesting is not recommended for women younger than 30 years because of the very high

Table 1. Screening Methods for Cervical Cancer for the General Population: Joint Recommendations of the American Cancer Society, the American Society for Colposcopy and Cervical Pathology, and the American Society for Clinical Pathology* ⇐

Population	Recommended Screening Method	Comment
Women younger than 21 years	No screening	
Women aged 21–29 years	Cytology alone every 3 years	
Women aged 30–65 years	Human papillomavirus and cytology cotesting (preferred) every 5 years Cytology alone (acceptable) every 3 years	Screening by HPV testing alone is not recommended*
Women older than 65 years	No screening is necessary after adequate negative prior screening results	Women with a history of CIN 2, CIN 3, or adenocarcinoma in situ should continue routine age-based screening for a total of 20 years after spontaneous regression or appropriate management of CIN 2, CIN 3, or adenocarcinoma in situ
Women who underwent total hysterectomy	No screening is necessary	Applies to women without a cervix and without a history of CIN 2, CIN 3, adenocarcinoma in situ, or cancer in the past 20 years
Women vaccinated against HPV	Follow age-specific recommendations (same as unvaccinated women)	

Abbreviations: CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus.

*After the Joint Recommendations were published, a test for screening with HPV testing alone was approved by the U.S. Food and Drug Administration. Gynecologic care providers using this test should follow the interim guidance developed by the American Society for Colposcopy and Cervical Pathology and the Society for Gynecologic Oncology (Huh WK, Ault KA, Chelmow D, Davey DD, Goulart RA, Garcia FA, et al. Use of primary high-risk human papillomavirus testing for cervical cancer screening: interim clinical guidance. Obstet Gynecol 2015;125:330–7.).

Modified from Saslow D, Solomon D, Lawson HW, Killackey M, Kulasingam SL, Cain J, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. ACS-ASCCP-ASCP Cervical Cancer Guideline Committee. CA Cancer J Clin 2012;62:147–72.

prevalence of high-risk HPV infections and the low incidence of cervical cancer in sexually active women in this age group (6, 86). Use of cotesting in women younger than 30 years largely would detect transient HPV infection without carcinogenic potential. In women younger than 30 years, the increased sensitivity and decreased specificity of cotesting would result in more testing than would cytology screening alone, without an appreciable decrease in cancer incidence (87).

Women aged 30 years and older with a negative cervical cytology screening result and a negative high-risk HPV test result have been shown to be at extremely low risk of developing CIN 2 or CIN 3 during the next 4–6 years (88). This risk was much lower than the risk for women who had only a negative cytology test result (85). In the Kaiser Permanente Northern California cohort, the 5-year risk of CIN 3+ was 0.26 in women with negative cytology alone and 0.08 in women with a negative cotest result (89).

Three randomized trials have compared cotesting with cytology screening alone in women aged 30–65 years (90–92). Each of the trials had a complex protocol and differed in the way that women with HPV-positive test results were evaluated. In each trial, cotesting detected an increased proportion of high-grade dysplasia in the first round of screening and a low rate of cancer with subsequent testing with cytology screening alone in the second round. The first trial demonstrated a statistically significant reduction of CIN 3 or cancer detection in the second round of screening, and a second study demonstrated a statistically significant reduction from 0.03% to 0% in the second phase of screening (90, 91). The difference in the rate of cancer detection was not reported in the third trial (92).

Cytology alone has been much less effective for the detection of adenocarcinoma of the cervix than for the detection of squamous cancer (93). Cotesting has the additional advantage of better detection of adenocarcinoma of the cervix and its precursors than cytology screening alone (94, 95).

It is important to educate patients about the nature of cervical cancer screening, its limitations, and the rationale for prolonging the screening interval. Regardless of the frequency of cervical cancer screening, patients should be counseled that annual well-woman visits are recommended even if cervical cancer screening is not performed at each visit (96).

▶ *What is the optimal frequency of cervical cytology screening for women aged 21–29 years?*

Few studies have been performed that specifically address the interval for screening women aged 21–29 years. A modeling study that examined outcomes for women aged 20 years and screened over a 10-year

period predicted that the number of colposcopy procedures would be reduced by approximately one half (187 per 1,000 women versus 403 per 1,000 women) if these women were screened every 3 years rather than annually, with marginal difference in lifetime cancer risk (0.69% versus 0.33%) (70). These results are similar to those reported in a study that compared outcomes associated with screening every 1 year, 2 years, or 3 years (97). Compared with screening every 3 years, screening every 2 years was associated with negligible change in risk of cancer (37 cases per 100,000 women versus 39 cases per 100,000 women) and more colposcopy procedures (176 procedures per 100,000 women versus 134 procedures per 100,000 women). A U.K. study noted no difference in risk between women aged 20–39 years with cervical cancer who had been screened 2 years or 3 years after their last negative test result (98). Annual screening leads to a very small increase in cases of cancer prevented at the cost of a very large excess of procedures and treatments and should not be performed. Because 2-year and 3-year testing intervals appear to be associated with similar reductions in risk of cancer, and a 3-year testing interval requires less additional testing, screening should be performed every 3 years in the 21–29-year age group. Annual screening should not be performed.

▶ *What is the optimal frequency of cervical cytology screening for women aged 30–65 years?*

In women aged 30–65 years, cotesting with cervical cytology screening and HPV testing is preferred and should be performed every 5 years. If screening is performed with cervical cytology alone, it can be done with either conventional or liquid-based cytology collection methods and should be performed every 3 years. Annual screening should not be performed.

The increased sensitivity of cotesting compared with cytology screening alone allows for greater detection of CIN 3 (6, 88). However, the decreased specificity results in the need for more follow-up testing. The decrease in cancer incidence achieved by 3-year cytology screening alone is the standard of care and considered acceptable. Using this as a benchmark, performing cotesting every 5 years achieves slightly lower rates of cancer, with less screening and fewer follow-up colposcopy procedures. A pooled analysis of seven European studies reported a 0.28% risk of CIN 3 or cancer 6 years after a negative cotesting result compared with a 0.51% risk of CIN 3 or cancer 3 years after a negative result from cytology testing alone (88). In the Kaiser Permanente Northern California cohort, the 3-year risk of CIN 3+ was 0.16

in women with a negative result from cytology testing alone, and the 5-year risk was 0.08 in women with a negative cotest result (89). The Agency for Healthcare Research and Quality has performed modeling studies of cases of cancer, deaths, and harms (as measured by colposcopy) (97). In three separate models over a wide range of assumptions, cotesting every 5 years compared with cytology screening alone every 3 years was associated with a similar number of or fewer cases of cancer (6.23–7.39 versus 5.98–8.97 per 1,000 women over a lifetime), number of deaths related to cancer (1.10–1.35 versus 0.95–1.55 per 1,000 women over a lifetime), and number of colposcopy procedures (626–907 versus 416–1,090 per 1,000 women over a lifetime).

Cytology screening alone is an acceptable alternative to cotesting and can be continued every 3 years until age 65 years. Studies over the past several decades have shown that in an organized program of cervical cancer screening, annual cytology examinations offer no net advantage over screening performed at 2-year or 3-year intervals (98–101). As in younger women, modeling studies showed that 1-year and 3-year screening intervals yielded low cervical cancer rates (70, 97). Cancer rates with a screening interval of every 3 years were slightly higher but were achieved with far fewer colposcopy procedures. Decision analyses demonstrate that screening every 3 years with cytology alone or screening every 5 years with cotesting provides a reasonable balance between the benefits and burdens of screening (97). The consensus conference review for the ACS, ASCCP, and the ASCP cervical cancer screening guidelines found inadequate high-quality data to recommend altering the screening interval based on prior negative cytology results in any age group (6). A matched case–control study calculated the risk of invasive cancer at different screening intervals and reported that the risk was not altered by a history of a prior abnormal cytology result or the number of previous normal screening test results (102).

▶ *At what age is it appropriate to discontinue screening?*

Screening by any modality should be discontinued after age 65 years in women with evidence of adequate negative prior screening test results and no history of CIN 2 or higher. Adequate negative prior screening test results are defined as three consecutive negative cytology results or two consecutive negative cotest results within the previous 10 years, with the most recent test performed within the past 5 years. Women with a history of CIN 2, CIN 3, or adenocarcinoma in situ should continue screening for a total of 20 years after spontaneous regression or appropriate management of CIN 2, CIN 3,

or adenocarcinoma in situ, even if it extends screening past age 65 years.

Women aged 65 years and older do get cervical cancer. Women in this age group represent 14.1% of the U.S. female population but have 19.6% of the new cases of cervical cancer (1, 103). However, as in younger women, most cases of cervical cancer occur in unscreened or inadequately screened women (104).

Because cervical cancer occurs a median of 15–25 years after HPV infection, screening women in this age group would prevent very few cases of cancer. Modeling studies suggest that, in women screened with cytology every 3 years until age 65 years, continued screening every 3 years until age 90 years in 1,000 women would prevent approximately 1.6 cases of cancer and 0.5 cancer-related deaths (97). This slight gain would come at significant cost, including an increase in required colposcopy procedures. Given the low risk of progression to cancer in women in this age group with newly acquired infection, there is no need to resume screening, even if a woman has a new sexual partner.

To further complicate screening in this age group, epithelial atrophy, common after menopause, likely predisposes women to false-positive cytology screening test results. One study noted an extremely low positive predictive value of abnormal cervical cytology test results when performed in postmenopausal women (105). Most positive Pap test results were false positives and likely would be followed with additional procedures, anxiety, and expense.

▶ *When is it appropriate to discontinue screening for women who have had a total hysterectomy?*

In women who have had a hysterectomy with removal of the cervix (total hysterectomy) and have never had CIN 2 or higher, routine cytology screening and HPV testing should be discontinued and not restarted for any reason.

Primary vaginal cancer is the rarest of the gynecologic malignancies (2). Women who have had a total hysterectomy and have no history of CIN 2 or higher are at very low risk of developing vaginal cancer. Cytology screening in this group has a small chance of detecting an abnormality, and the test has a very low positive predictive value. A systematic review aggregated data from 19 studies that involved 6,543 women who had a hysterectomy in which the cervix was not affected by CIN and 5,037 women who had a hysterectomy in which the cervix was affected by CIN 3 (106). On follow-up, among the women with hysterectomy who did not have CIN, 1.8% had an abnormal vaginal cytology screening

result, and 0.12% had vaginal intraepithelial neoplasia on biopsy. No cases of cancer were reported. Continued vaginal cytology examinations in this population of women are not effective, particularly because of the very low risk of developing vaginal cancer, and will cause inconvenience, anxiety, and overtreatment.

Women who had high-grade cervical intraepithelial lesions before hysterectomy with removal of the cervix can develop recurrent intraepithelial neoplasia or carcinoma at the vaginal cuff years after the procedure (107, 108). In a systematic review, in a group of women with prior CIN 3, abnormal cytology results were reported in 14.1% of cases, but vaginal intraepithelial neoplasia on biopsy was rare (1.7%), and only one case of cancer was reported, which was diagnosed 3 years after hysterectomy (106). Women should continue to be screened if they have had a total hysterectomy and have a history of CIN 2 or higher in the past 20 years or cervical cancer at any point. The role of HPV testing has not been clarified in this population. Continued screening for 20 years is recommended in women who still have a cervix and a history of CIN 2 or higher (40). Therefore, screening with cytology alone every 3 years for 20 years after the initial posttreatment surveillance period seems to be reasonable for these women.

▶ *What is the role for cervical cancer screening with HPV testing alone?*

In April 2014, the FDA modified the labeling of a currently marketed HPV test to include the additional indication of primary cervical cancer screening (HPV primary screening) (109). Primary HPV screening was explicitly not recommended at the time of the 2011 joint ACS, ASCCP, and ASCP guidelines. This recommendation was based on concerns about the poor specificity of HPV testing, the lack of a proven triage algorithm to determine which patients with positive tests required diagnostic evaluations, and the potential for excess diagnostic evaluations and treatments. Since that time, a large U.S.-based study of HPV primary screening, known as the Addressing the Need for Advanced HPV Diagnostics trial, was conducted and validated an effective triage algorithm (110). In the trial, positive specimens underwent HPV genotyping. If a specimen was positive for HPV-16 or HPV-18, colposcopy was performed. If a specimen was negative for HPV-16 and HPV-18, cytology testing was performed on the specimen, and if the results were abnormal, colposcopy was performed. If cytology results were normal, repeat cotesting was performed in 1 year.

Based on the HPV test's equivalent or superior effectiveness for primary cervical cancer screening compared with cytology alone in the Addressing the Need

for Advanced HPV Diagnostics trial, the FDA modified the labeling of the test to include an indication for its use for primary screening in women starting at age 25 years. Cytology alone and cotesting remain the options specifically recommended in current major society guidelines. In 2015, ASCCP and SGO published interim guidance for the use of the FDA-approved HPV test for primary cervical cancer screening (8). The interim guidance panel concluded that because of its equivalent or superior effectiveness, in women 25 years and older, the FDA-approved primary HPV screening test can be considered as an alternative to current cytology-based cervical cancer screening methods (8).

If screening with primary HPV testing is used, it should be performed as per the ASCCP and SGO interim guidance (8), which clarifies a number of important issues not specified in the product labeling. The test should not be used in women younger than 25 years; these women should continue to be screened with cytology alone. Rescreening after a negative primary HPV screening result should occur no sooner than every 3 years. Positive test results should be triaged with genotyping for HPV-16 and HPV-18, and if the genotyping test results are negative, with cytology testing. If genotyping and cytology test results are negative, patients should have follow-up testing in 1 year.

Although not explicitly stated in the interim guidance, several other points are important. Screening should stop at age 65 years in women with negative screening histories. The primary HPV screening test should not be used in women who no longer have a cervix. Which test to perform at 1-year follow-up in women with positive HPV primary screening test results and negative genotyping and cytology test results is not stated, but cotesting is reasonable. There is no guidance for use of the test in women with HIV or who are immunocompromised. Only one specific HPV test has FDA approval for primary screening (109). No other tests have undergone validation. If primary screening is performed, it should be done with the approved test.

▶ *How should ASC-US cytology and negative HPV test results be managed?*

Women with ASC-US cytology and negative HPV test results, whether from reflex HPV testing or cotesting, have a low risk of CIN 3, but it is slightly higher than the risk in women with a negative cotest result, and it is recommended that they have cotesting in 3 years (40, 111) (Table 2). This recommendation is a change from the 2011 joint ACS, ASCCP, and ASCP cervical cytology screening guidelines, which recommended routine screening for these women (6).

The management of ASC-US has been associated with much confusion. Frequently, it has been managed as if it is a diagnosis, but it actually represents diagnostic uncertainty, comprising a mix of patients who have squamous intraepithelial lesions and others who do not.

Table 2. Management of Cervical Cancer Screening Results ⇐

Screening Method	Result	Management
Cytology screening alone	Cytology negative	Screen again in 3 years
	ASC-US cytology and reflex HPV negative	Cotest in 3 years
	All others	Refer to ASCCP guidelines*
Cotesting	Cytology negative, HPV negative	Screen again in 5 years
	ASC-US cytology, HPV negative	Screen again in 3 years
	Cytology negative, HPV positive	Option 1: 12-month follow-up with cotesting
		Option 2: Test for HPV-16 or HPV-18 genotypes
		• If positive results from test for HPV-16 or HPV-18, referral for colposcopy
		• If negative results from test for HPV-16 and HPV-18, 12-month follow-up with cotesting
	All others	Refer to ASCCP guidelines*

Abbreviations: ASCCP, American Society for Colposcopy and Cervical Pathology; ASC-US, atypical squamous cells of undetermined significance; HPV, human papillomavirus.

*Massad LS, Einstein MH, Huh WK, Katki HA, Kinney WK, Schiffman M, et al, for the 2012 ASCCP Consensus Guidelines Conference. 2012 Updated Consensus Guidelines for the Management of Abnormal Cervical Cancer Screening Tests and Cancer Precursors. J Low Genit Tract Dis 2013;17:S1–S27.

Modified from Saslow D, Solomon D, Lawson HW, Killackey M, Kulasingam SL, Cain J, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. ACS-ASCCP-ASCP Cervical Cancer Guideline Committee. CA Cancer J Clin 2012;62:147–72, with additional modifications based on Massad LS, Einstein MH, Huh WK, Katki HA, Kinney WK, Schiffman M, et al, for the 2012 ASCCP Consensus Guidelines Conference. 2012 Updated Consensus Guidelines for the Management of Abnormal Cervical Cancer Screening Tests and Cancer Precursors. J Low Genit Tract Dis 2013;17:S1–S27.

Human papillomavirus testing is a very effective method of triage for an ASC-US cytology result. With a negative HPV test result, the risk of a precancerous lesion is extremely low. In the Kaiser Permanente Northern California cohort, 5-year risks of CIN 3+ and cancer in women aged 30–64 years with ASC-US cytology and a negative HPV test result were 0.43% and 0.05%, respectively, which is significantly higher than the 5-year risks for women with negative cotest results (0.08% and 0.011%, respectively) (112). The risk of CIN 3+ actually was comparable to the risk among women with negative cytology test results alone; therefore (using the principle of managing test results with similar risk in the same way), the 2012 ASCCP Consensus Guidelines for the Management of Abnormal Cervical Cancer Screening Tests and Cancer Precursors (40) recommend that women aged 30–65 years should have follow-up cotesting in 3 years rather than in 5 years, as originally recommended in the 2011 screening guidelines (6). If their 3-year cotest results are negative, they then can return to age-appropriate routine screening (40, 111).

▶ How should cytology-negative, HPV-positive cotest results be managed?

In a recent study, cytology-negative and HPV-positive cotest results occurred in 3.7% of women older than 30 years (94). Counseling and management of women with these results is a significant issue with cotesting. The risk of significant pathology is small in this group. A summary of 11 prospective studies with 1–16-year follow-up noted a 12-month risk of CIN 3 of 0.8–4.1% (6). In the Kaiser Permanente Northern California cohort, 5-year risks of CIN 3+ and cancer were 4.5% and 0.34%, respectively (112). This low risk of a premalignant lesion makes colposcopy a poor diagnostic option for this population.

Cytology-negative, HPV-positive cotest results in women who are 30 years and older should be managed in one of two ways (Fig. 1):

1. Repeat cotesting in 12 months. If the repeat cervical cytology test result is ASC-US or higher or the HPV test result is still positive, the patient should be referred for colposcopy. Otherwise, the patient should have cotesting in 3 years. The level of cytology at which a diagnostic evaluation should be performed changed from the previously recommended LSIL to any abnormality (ASC-US or higher) with the 2012 ASCCP revised guidelines for management of abnormal cervical cancer screening test results (40).

2. Immediate HPV genotype-specific testing for HPV-16 and HPV-18 can be performed. Women with positive test results for either HPV genotype should be referred directly for colposcopy. Women with negative test results for both HPV genotypes should be cotested in 12 months, with management of results as described in the 2012 ASCCP revised guidelines for the management of abnormal cervical cancer screening test results (40, 111).
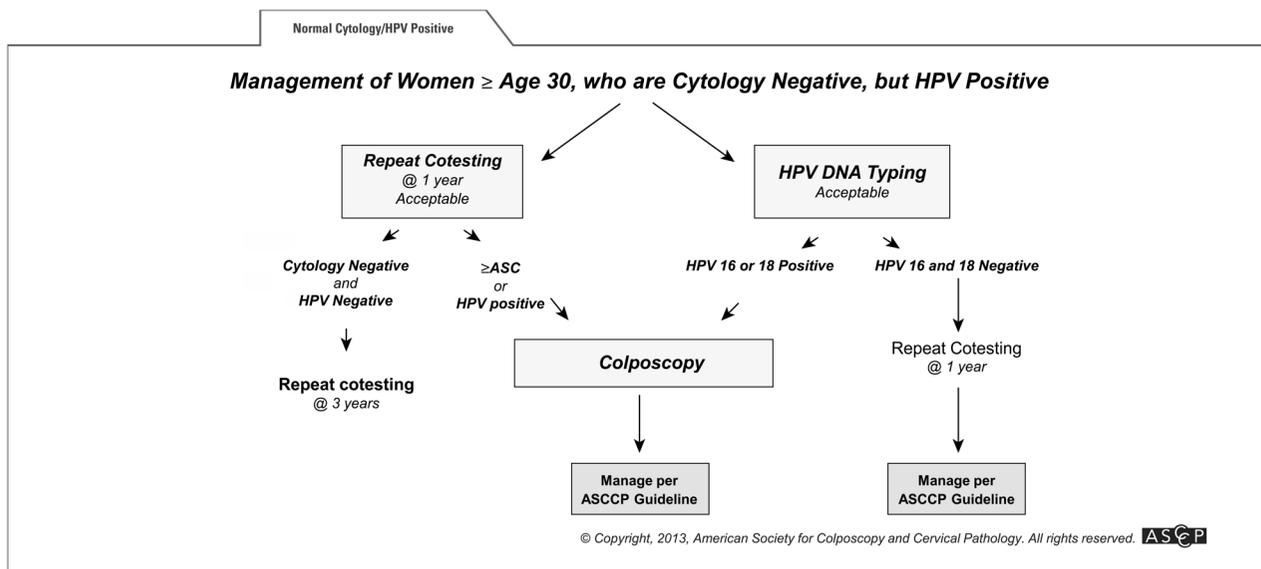
Figure 1. Management of women 30 years and older, who are cytology negative, but HPV positive. Abbreviations: ASC, atypical squamous cells; ASCCP, American Society for Colposcopy and Cervical Pathology; HPV, human papillomavirus. (Reprinted from Massad LS, Einstein MH, Huh WK, Katki HA, Kinney WK, Schiffman M, et al, for the 2012 ASCCP Consensus Guidelines Conference. 2012 Updated Consensus Guidelines for the Management of Abnormal Cervical Cancer Screening Tests and Cancer Precursors. J Low Genit Tract Dis 2013;17:S1–S27.) ⇐

No studies directly compare different management options for women with HPV-positive and cytology-negative test results. The rationale for repeat cotesting comes from results of cohort studies, which show that most transient infections clear by 12 months. A cohort study reported that in 60% of women with HPV-positive, liquid-based, cytology-negative test results, the infection was cleared in a median of 6 months (25). A separate cohort study reported that in 67% of patients, the HPV infection was cleared by 1 year (29). Of women who had infections that persisted at 1 year, 21% developed CIN 2 or higher within 30 months. In the Kaiser Permanente Northern California cohort, 47% of women remained HPV positive at 1 year. At the time of repeat testing, any abnormal cotest result was associated with higher risk than the same abnormality at baseline (112). Repeat cotesting in 1 year allows most women with transient infection and no carcinogenic risk sufficient time for the HPV infection to clear and identifies a smaller group at higher risk of precancerous lesions to undergo colposcopy. The higher risks noted in the Kaiser cohort justify colposcopy for any abnormality at this point and 3-year follow-up in patients whose cotest result has returned to normal.

The FDA-approved HPV tests may be used to determine if a woman with a positive cotest result for HPV has HPV-16 or HPV-18. If HPV-16 or HPV-18 is detected, the risk of CIN 3 approaches 10% within a few years, a risk high enough to justify colposcopy (18, 113, 114). These tests may be used as an alternative in patients with HPV-positive, cytology-negative cotest results, and if positive, the patient is referred for immediate colposcopy. If results are negative, cotesting is repeated in 1 year because some risk from other genotypes still exists, and results are managed as indicated in Figure 1 (40).

▶ *Should administration of the HPV vaccine change how cervical cancer screening is performed?*

Women who have received the HPV vaccine should be screened according to the same guidelines as women who have not been vaccinated. The bivalent and quadrivalent HPV vaccines immunize against only two of the carcinogenic genotypes, HPV-16 and HPV-18. These two genotypes are responsible for up to approximately 75% of all cases of cervical cancer. However, despite data suggesting that the HPV vaccine provides nearly 100% protection against CIN caused by these two genotypes in previously uninfected women, 30% of cases of cervical cancer from other HPV genotypes not included

in the vaccine are expected to continue to occur (115, 116). The 9-valent HPV vaccine immunizes against five additional high-risk subtypes but still does not cover all subtypes. Current recommendations from ACIP and the American College of Obstetricians and Gynecologists allow for vaccination through age 26 years, a time when many women may already have acquired the virus, which significantly decreases the efficacy of the vaccine (66, 67). The rate of vaccine administration is far from 100%, and given the absence of a vaccine registry in the United States, it often is difficult to ascertain who has been vaccinated or who has received all three doses of the vaccine (117, 118). Long-term efficacy of the vaccine remains incompletely established. Although HPV vaccination is an important step toward cervical cancer prevention, it does not remove the need for routine cervical cancer screening.

▶ *Are any alternative cervical cancer screening strategies recommended for specific populations?*

Certain risk factors have been associated with CIN in observational studies. Women with any of the following risk factors may require more frequent cervical cancer screening than recommended in the routine screening guidelines, which were intended for average-risk women:

- Women who are infected with HIV
- Women who are immunocompromised (such as those who have received solid organ transplants)
- Women who were exposed to diethylstilbestrol in utero
- Women previously treated for CIN 2, CIN 3, or cancer

The Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents recommends that women who are infected with HIV should have age-based cervical cancer screening as follows (68). For more information, see Practice Bulletin No. 167, *Gynecologic Care for Women and Adolescents With Human Immunodeficiency Virus*.

- Initiation of cervical cancer screening with cytology alone should begin within 1 year of onset of sexual activity or, if already sexually active, within the first year after HIV diagnosis but no later than 21 years of age.
- Cervical cancer screening in women who are infected with HIV should continue throughout a woman's lifetime (ie, not stopping at age 65 years).

- In women infected with HIV who are younger than 30 years, if the initial cytology screening result is normal, the next cytology screening should be in 12 months. If the results of three consecutive annual cervical cytology screenings are normal, follow-up cervical cytology screening should be every 3 years. Cotesting is not recommended for HIV-infected women younger than 30 years.

- Women infected with HIV who are 30 years and older can be screened with cytology alone or cotesting. After women screened with cytology alone have had three consecutive annual test results that are normal, follow-up screening can be every 3 years. Women infected with HIV who have one negative cotest result (normal cytology and HPV negative) can have their next cervical cancer screening in 3 years.

- In women with HIV infection, cotesting results that are cytology negative but HPV positive are managed as in the general population (see "*How should cytology-negative, HPV-positive cotest results be managed?*").

- Women with HIV infection who have cervical cytology results of LSIL or worse should be referred for colposcopy.

- For women with HIV infection who are 21 years or older and have ASC-US test results, if reflex HPV testing results are positive, referral to colposcopy is recommended. If HPV testing is not available, repeat cervical cytology in 6–12 months is recommended, and for any result of ASC-US or worse on repeat cytology, referral to colposcopy is recommended. Repeat cytology in 6–12 months, but not HPV testing, is recommended for HIV-infected women younger than 21 years with ASC-US test results. Although not explicitly stated in the Panel guidelines, women with HIV infection who have ASC-US, HPV-negative results (whether from reflex HPV testing or cotesting) can return to regular screening.

No studies or major society recommendations exist to guide cervical cancer screening in women who are immunocompromised because of non-HIV causes. Annual cytology traditionally has been performed in these women, but it is reasonable to extrapolate the recommendations for women with HIV infection to this group. Annual cervical cytology screening is reasonable for women exposed to diethylstilbestrol in utero.

Women treated in the past for CIN 2 or higher remain at risk of persistent or recurrent disease for at least 20 years after treatment. A meta-analysis demonstrated that women with a history of treatment for CIN 2 or higher remain at a 2.8-fold increased risk of invasive disease for up to 20 years after treatment (119). Because of this increased risk, women with a history of CIN 2 or higher should continue to undergo routine age-based screening for 20 years after the initial posttreatment surveillance period, even if it requires that screening continue past age 65 years (6, 40).

Summary of Recommendations and Conclusions

The following recommendations and conclusions are based on good and consistent scientific evidence (Level A):

▶ Cervical cancer screening should begin at age 21 years. With the exception of women who are infected with HIV or who are otherwise immunocompromised, women younger than 21 years should not be screened regardless of the age of sexual initiation or the presence of other behavior-related risk factors.

▶ Women aged 21–29 years should be tested with cervical cytology alone, and screening should be performed every 3 years. Cotesting should not be performed in women younger than 30 years. Annual screening should not be performed.

▶ For women aged 30–65 years, cotesting with cytology and HPV testing every 5 years is preferred; screening with cytology alone every 3 years is acceptable. Annual screening should not be performed.

▶ Liquid-based and conventional methods of cervical cytology collection are acceptable for screening.

▶ Screening by any modality should be discontinued after age 65 years in women with evidence of adequate negative prior screening test results and no history of CIN 2 or higher. Adequate negative prior screening test results are defined as three consecutive negative cytology results or two consecutive negative cotest results within the previous 10 years, with the most recent test performed within the past 5 years.

▶ In women who have had a hysterectomy with removal of the cervix (total hysterectomy) and have never had CIN 2 or higher, routine cytology screening and HPV testing should be discontinued and not restarted for any reason.

- ▶ Women with any of the following risk factors may require more frequent cervical cancer screening than recommended in the routine screening guidelines, which were intended for average-risk women:

  —Women who are infected with HIV

  —Women who are immunocompromised (such as those who have received solid organ transplants)

  —Women who were exposed to diethylstilbestrol in utero

  —Women previously treated for CIN 2, CIN 3, or cancer

The following recommendations are based on limited and inconsistent scientific evidence (Level B):

- ▶ Women with a history of CIN 2, CIN 3, or adenocarcinoma in situ should continue screening for a total of 20 years after spontaneous regression or appropriate management of CIN 2, CIN 3, or adenocarcinoma in situ, even if it extends screening past age 65 years.

- ▶ Women should continue to be screened if they have had a total hysterectomy and have a history of CIN 2 or higher in the past 20 years or cervical cancer at any point. Screening with cytology alone every 3 years for 20 years after the initial posttreatment surveillance period seems to be reasonable for these women.

- ▶ In women 25 years and older, the FDA-approved primary HPV screening test can be considered as an alternative to current cytology-based cervical cancer screening methods. Cytology alone and cotesting remain the options specifically recommended in current major society guidelines. If screening with primary HPV testing is used, it should be performed as per the ASCCP and SGO interim guidance.

- ▶ Women with ASC-US cytology and negative HPV test results, whether from reflex HPV testing or cotesting, have a low risk of CIN 3, but it is slightly higher than the risk in women with a negative cotest result, and it is recommended that they have cotesting in 3 years.

- ▶ Cytology-negative, HPV-positive cotest results in women who are 30 years and older should be managed in one of two ways:

  1. Repeat cotesting in 12 months. If the repeat cervical cytology test result is ASC-US or higher or the HPV test result is still positive, the patient should be referred for colposcopy. Otherwise, the patient should have cotesting in 3 years.

  2. Immediate HPV genotype-specific testing for HPV-16 and HPV-18 can be performed. Women with positive test results for either HPV genotype should be referred directly for colposcopy. Women with negative test results for both HPV genotypes should be cotested in 12 months, with management of results as described in the 2012 ASCCP revised guidelines for the management of abnormal cervical cancer screening test results.

The following recommendation is based primarily on consensus and expert opinion (Level C):

- ▶ Women who have received the HPV vaccine should be screened according to the same guidelines as women who have not been vaccinated.

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The MEDLINE database, the Cochrane Library, and the American College of Obstetricians and Gynecologists' own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 1990–January 2015. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

I   Evidence obtained from at least one properly designed randomized controlled trial.
II-1 Evidence obtained from well-designed controlled trials without randomization.
II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
III   Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.